

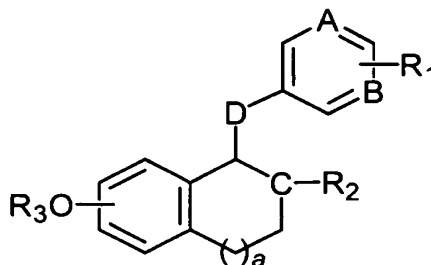
Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of claims:

1-33. (Canceled)

34. (Currently Amended) A method for modulating ER- β in a breast cancer cell or bone cancer cell expressing ER- β , comprising contacting the cell with an effective amount of a compound having the structure:



or a pharmaceutically acceptable salt thereof;

wherein

a is 0, 1 or 2;

A, B and C are independently CH, CR or N;

D is $-(CH_2)_r-$ or $-(CH_2)_nC(=O)(CH_2)_m-$;

R_1 represents one or two substituents independently selected from -X-Y;

R_2 is C_{1-8} alkyl, C_{6-12} aryl, C_{7-12} aralkyl, $-C(=O)R_5$, a five- or six-membered heterocycle or heterocyclealkyl containing up to two heteroatoms selected from O, NR_c and $S(O)_q$, or a bicyclic ring system contain a five- or six-membered heterocycle fused to phenyl, wherein each of the above groups are optionally substituted with one to three substituents independently selected from -X-Y or R_4 ; and

R_3 is hydrogen, $-R_6$, $-(CH_2)_sC(=O)R_6$, $-(CH_2)_sC(=O)OR_6$, $-(CH_2)_sC(=O)NR_6R_7$, $-(CH_2)_sC(=O)NR_6(CH_2)_nC(=O)R_7R_8$, $-(CH_2)_sNR_6C(=O)R_7$, $-(CH_2)_sNR_6C(=O)NR_7R_8$, $-(CH_2)_sNR_6R_7$, $-(CH_2)_sOR_6$, $-(CH_2)_sSO_qR_6$ or $-(CH_2)_sSO_2NR_6R_7$;

and wherein

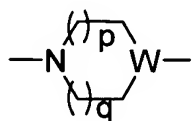
R_4 is at each occurrence independently halogen, hydroxy, carboxy, C_{1-6} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, acyloxy, C_{1-4} thio, C_{1-4} alkylsulfinyl, C_{1-4} alkylsulfonyl, (hydroxy) C_{1-4} alkyl, C_{6-12} aryl, C_{7-12} aralkyl, $-C(=O)OH$, $-C(=O)OR$, $-OC(=O)R$, $-C(=O)NHR$, $-C(=O)NRR$,

-C(=O)NHOR, -SO₂NHR, -NHSO₂R, -CN, -NO₂, C₁₋₄alkylamino, C₁₋₄dialkylamino, -NHC(=O)R, NHC(=O)(CH₂)_s(five- or six-membered heterocycle), a five- or six-membered heterocycle, or a five- or six-membered heterocycle fused to phenyl;

R₅, R₆, R₇ and R₈ are at each occurrence independently hydrogen, C₁₋₈alkyl, C₆₋₁₂aryl, C₇₋₁₂aralkyl, or a five- or six-membered heterocycle or heterocyclealkyl containing up to two heteroatoms selected from O, NR_c and S(O)_q, wherein each of the above groups are optionally substituted with one to three substituents independently selected from R₄;

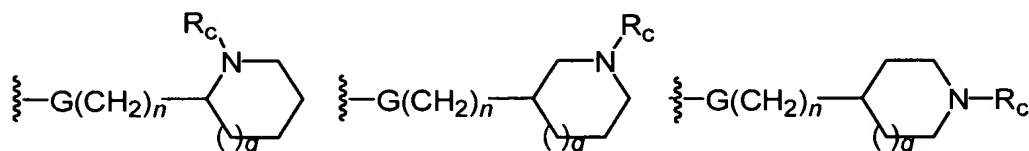
X is at each occurrence independently a direct bond; -(CH₂)_nZ(CH₂)_m-; -O(CH₂)_nZ(CH₂)_m-; -S(CH₂)_nZ(CH₂)_m-; -NR_c(CH₂)_nZ(CH₂)_m-; -O(CH₂)_nCR_aR_b-; -NR_c(CH₂)_nCR_aR_b-; -OCHR_cCHR_d-; or -SCHR_cCHR_d-;

Y is at each occurrence independently halogen; -R_e; -NR_eR_f;

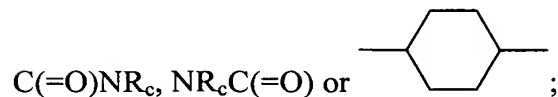


, optionally fused on adjacent carbon atoms with one or two phenyl or cycloalkyl rings, and with each carbon optionally and independently substituted with carbonyl or with one or two substituents independently selected from R₄, with any two R₄ substituents on a single carbon atom optionally being taken together to form a five- or six-membered heterocycle, and with each nitrogen atom optionally and independently substituted with R₄, wherein W is -NR_e-, -O-, -S- or -CR_eR_f-; or a bridged or fused C₅₋₁₂bicyclic amine optionally substituted with one to three substituents independently selected from R₄;

or where -X-Y is



Z is CH₂, CH=CH, C≡C, O, NR_c, S(O)_q, C(=O), C(OH)R_c, C(=O)NR_c, NR_cC(=O),



G is O, S or NR_e;

n and m are at each occurrence independently 0, 1, 2 or 3;

p is at each occurrence independently 1, 2 or 3;

q is at each occurrence independently 0, 1 or 2;

r is at each occurrence independently 1, 2, 3, 4 or 5;

s is at each occurrence independently 0, 1, 2, 3 or 4;

R is at each occurrence independently C₁₋₆alkyl;

R_a and R_b are at each occurrence independently C₁₋₈alkyl or taken together form a C₃₋₈cyclic alkyl;

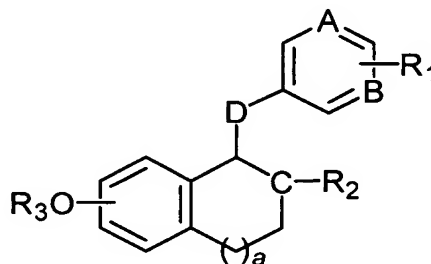
R_c and R_d are at each occurrence independently hydrogen or C₁₋₄alkyl; and

R_e and R_f are at each occurrence independently hydrogen, C₆₋₁₂aryl, C₁₋₈alkyl, C₇₋₁₂aralkyl, a five- or six-membered heterocycle, or a five- or six membered heterocycle fused to phenyl; or wherein R_e or R_f form a 3-8 membered nitrogen-containing heterocyclic alkyl with R_a or R_b; and wherein each R_e and R_f are optionally substituted with up to three substituents independently selected from R₄.

35. (Previously Presented) The method of claim 34 wherein the cell preferentially expresses ER-β over ER-α.

36. (Currently Amended) The method of claim 35 wherein the cell is ~~bone, bladder, uterus, ovary, prostate, testis, epididymis, gastrointestinal tract, kidney, a breast, eye, heart, vessel wall, immune system, lung, pituitary, hippocampus or hypothalamus~~ cancer cell.

37. (Currently Amended) A method for modulating ER-β in breast cancer tissue or bone cancer tissue expressing ER-β, comprising contacting the tissue with an effective amount of a compound having the structure:



or a pharmaceutically acceptable salt thereof;

wherein

a is 0, 1 or 2;

A, B and C are independently CH, CR or N;

D is $-(CH_2)_r-$ or $-(CH_2)_nC(=O)(CH_2)_m-$;

R₁ represents one or two substituents independently selected from -X-Y;

R₂ is C₁₋₈ alkyl, C₆₋₁₂aryl, C₇₋₁₂aralkyl, $-C(=O)R_5$, a five- or six-membered heterocycle or heterocyclealkyl containing up to two heteroatoms selected from O, NR_c and S(O)_q, or a bicyclic ring system contain a five- or six-membered heterocycle fused to phenyl, wherein each of the above groups are optionally substituted with one to three substituents independently selected from -X-Y or R₄; and

R₃ is hydrogen, -R₆, $-(CH_2)_sC(=O)R_6$, $-(CH_2)_sC(=O)OR_6$, $-(CH_2)_sC(=O)NR_6R_7$, $-(CH_2)_sC(=O)NR_6(CH_2)_nC(=O)R_7R_8$, $-(CH_2)_sNR_6C(=O)R_7$, $-(CH_2)_sNR_6C(=O)NR_7R_8$, $-(CH_2)_sNR_6R_7$, $-(CH_2)_sOR_6$, $-(CH_2)_sSO_qR_6$ or $-(CH_2)_sSO_2NR_6R_7$;

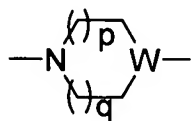
and wherein

R₄ is at each occurrence independently halogen, hydroxy, carboxy, C₁₋₆alkyl, C₁₋₄alkoxy, C₁₋₄haloalkyl, acyloxy, C₁₋₄thio, C₁₋₄alkylsulfinyl, C₁₋₄alkylsulfonyl, (hydroxy)C₁₋₄alkyl, C₆₋₁₂aryl, C₇₋₁₂aralkyl, $-C(=O)OH$, $-C(=O)OR$, $-OC(=O)R$, $-C(=O)NHR$, $-C(=O)NRR$, $-C(=O)NHOR$, $-SO_2NHR$, $-NHSO_2R$, $-CN$, $-NO_2$, C₁₋₄alkylamino, C₁₋₄dialkylamino, $-NHC(=O)R$, $NHC(=O)(CH_2)_s$ (five- or six-membered heterocycle), a five- or six-membered heterocycle, or a five- or six-membered heterocycle fused to phenyl;

R₅, R₆, R₇ and R₈ are at each occurrence independently hydrogen, C₁₋₈alkyl, C₆₋₁₂aryl, C₇₋₁₂aralkyl, or a five- or six-membered heterocycle or heterocyclealkyl containing up to two heteroatoms selected from O, NR_c and S(O)_q, wherein each of the above groups are optionally substituted with one to three substituents independently selected from R₄;

X is at each occurrence independently a direct bond; $-(CH_2)_nZ(CH_2)_m-$; $-O(CH_2)_nZ(CH_2)_m-$; $-S(CH_2)_nZ(CH_2)_m-$; $-NR_c(CH_2)_nZ(CH_2)_m-$; $-O(CH_2)_nCR_aR_b-$; $-NR_c(CH_2)_nCR_aR_b-$; $-OCHR_cCHR_d-$; or $-SCHR_cCHR_d-$;

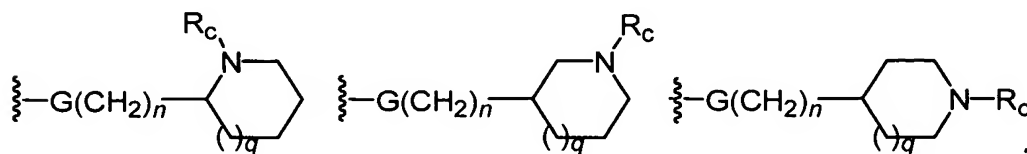
Y is at each occurrence independently halogen; -R_c; -NR_cR_f;



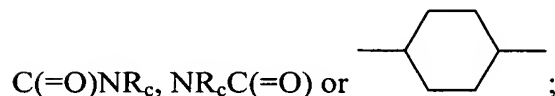
, optionally fused on adjacent carbon atoms with one or two phenyl or cycloalkyl rings, and with each carbon optionally and independently substituted with carbonyl or with one or two substituents independently selected from R₄, with any two R₄ substituents on a single carbon atom optionally being taken together to form a five- or six-membered heterocycle, and with each nitrogen atom optionally and independently substituted

with R_4 , wherein W is $-NR_e-$, $-O-$, $-S-$ or $-CR_eR_f-$; or a bridged or fused C_{5-12} bicyclic amine optionally substituted with one to three substituents independently selected from R_4 ;

or where $-X-Y$ is



Z is CH_2 , $CH=CH$, $C\equiv C$, O , NR_c , $S(O)_q$, $C(=O)$, $C(OH)R_c$, $C(=O)NR_c$, $NR_cC(=O)$,



G is O , S or NR_e ;

n and m are at each occurrence independently 0, 1, 2 or 3;

p is at each occurrence independently 1, 2 or 3;

q is at each occurrence independently 0, 1 or 2;

r is at each occurrence independently 1, 2, 3, 4 or 5;

s is at each occurrence independently 0, 1, 2, 3 or 4;

R is at each occurrence independently C_{1-6} alkyl;

R_a and R_b are at each occurrence independently C_{1-8} alkyl or taken together form a C_{3-8} cyclic alkyl;

R_c and R_d are at each occurrence independently hydrogen or C_{1-4} alkyl; and

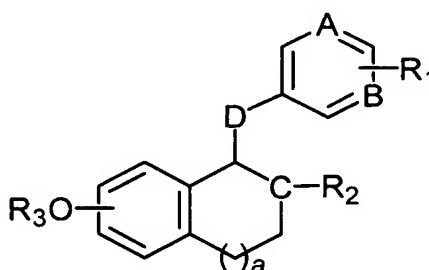
R_e and R_f are at each occurrence independently hydrogen, C_{6-12} aryl, C_{1-8} alkyl, C_{7-12} aralkyl, a five- or six-membered heterocycle, or a five- or six membered heterocycle fused to phenyl; or wherein R_e or R_f form a 3-8 membered nitrogen-containing heterocyclic alkyl with R_a or R_b ; and wherein each R_e and R_f are optionally substituted with up to three substituents independently selected from R_4 .

38. (Original) The method of claim 37 wherein the tissue preferentially expresses ER- β over ER- α .

39. (Currently Amended) The method of claim 38 wherein the tissue is of bone, bladder, uterus, ovary, prostate, testis, epididymis, gastrointestinal tract, kidney, breast, eye, heart, vessel wall, immune system, lung, pituitary, hippocampus or hypothalamus.

40. (Canceled)

41. (Currently Amended) A method for treating an estrogen-related condition comprising administering to a patient in need thereof an effective amount of a compound having the structure:



or a pharmaceutically acceptable salt thereof;

wherein

a is 0, 1 or 2;

A, B and C are independently CH, CR or N;

D is $-(CH_2)_r-$ or $-(CH_2)_nC(=O)(CH_2)_m-$;

R_1 represents one or two substituents independently selected from -X-Y;

R_2 is C_{1-8} alkyl, C_{6-12} aryl, C_{7-12} aralkyl, $-C(=O)R_5$, a five- or six-membered heterocycle or heterocyclealkyl containing up to two heteroatoms selected from O, NR_c and $S(O)_q$, or a bicyclic ring system contain a five- or six-membered heterocycle fused to phenyl, wherein each of the above groups are optionally substituted with one to three substituents independently selected from -X-Y or R_4 ; and

R_3 is hydrogen, $-R_6$, $-(CH_2)_sC(=O)R_6$, $-(CH_2)_sC(=O)OR_6$, $-(CH_2)_sC(=O)NR_6R_7$, $-(CH_2)_sC(=O)NR_6(CH_2)_nC(=O)R_7R_8$, $-(CH_2)_sNR_6C(=O)R_7$, $-(CH_2)_sNR_6C(=O)NR_7R_8$, $-(CH_2)_sNR_6R_7$, $-(CH_2)_sOR_6$, $-(CH_2)_sSO_qR_6$ or $-(CH_2)_sSO_2NR_6R_7$;

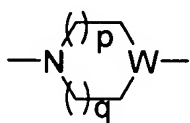
and wherein

R₄ is at each occurrence independently halogen, hydroxy, carboxy, C₁₋₆alkyl, C₁₋₄alkoxy, C₁₋₄haloalkyl, acyloxy, C₁₋₄thio, C₁₋₄alkylsulfinyl, C₁₋₄alkylsulfonyl, (hydroxy)C₁₋₄alkyl, C₆₋₁₂aryl, C₇₋₁₂aralkyl, -C(=O)OH, -C(=O)OR, -OC(=O)R, -C(=O)NHR, -C(=O)NRR, -C(=O)NHOR, -SO₂NHR, -NH₂SO₂R, -CN, -NO₂, C₁₋₄alkylamino, C₁₋₄dialkylamino, -NHC(=O)R, NHC(=O)(CH₂)_s(five- or six-membered heterocycle), a five- or six-membered heterocycle, or a five- or six-membered heterocycle fused to phenyl;

R₅, R₆, R₇ and R₈ are at each occurrence independently hydrogen, C₁₋₈alkyl, C₆₋₁₂aryl, C₇₋₁₂aralkyl, or a five- or six-membered heterocycle or heterocyclealkyl containing up to two heteroatoms selected from O, NR_c and S(O)_q, wherein each of the above groups are optionally substituted with one to three substituents independently selected from R₄;

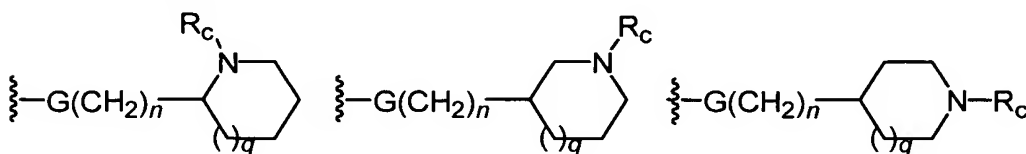
X is at each occurrence independently a direct bond; -(CH₂)_nZ(CH₂)_m-; -O(CH₂)_nZ(CH₂)_m-; -S(CH₂)_nZ(CH₂)_m-; -NR_c(CH₂)_nZ(CH₂)_m-; -O(CH₂)_nCR_aR_b-; -NR_c(CH₂)_nCR_aR_b-; -OCHR_cCHR_d-; or -SCHR_cCHR_d-;

Y is at each occurrence independently halogen; -R_e; -NR_eR_f;

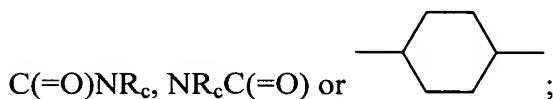


, optionally fused on adjacent carbon atoms with one or two phenyl or cycloalkyl rings, and with each carbon optionally and independently substituted with carbonyl or with one or two substituents independently selected from R₄, with any two R₄ substituents on a single carbon atom optionally being taken together to form a five- or six-membered heterocycle, and with each nitrogen atom optionally and independently substituted with R₄, wherein W is -NR_e-, -O-, -S- or -CR_eR_f-; or a bridged or fused C₅₋₁₂bicyclic amine optionally substituted with one to three substituents independently selected from R₄;

or where -X-Y is



Z is CH₂, CH=CH, C≡C, O, NR_c, S(O)_q, C(=O), C(OH)R_c, C(=O)NR_c, NR_cC(=O),



G is O, S or NR_e;

n and m are at each occurrence independently 0, 1, 2 or 3;

p is at each occurrence independently 1, 2 or 3;

q is at each occurrence independently 0, 1 or 2;

r is at each occurrence independently 1, 2, 3, 4 or 5;

s is at each occurrence independently 0, 1, 2, 3 or 4;

R is at each occurrence independently C₁₋₆alkyl;

R_a and *R_b* are at each occurrence independently C₁₋₈alkyl or taken together form a C₃₋₈cyclic alkyl;

R_c and *R_d* are at each occurrence independently hydrogen or C₁₋₄alkyl; and

R_e and *R_f* are at each occurrence independently hydrogen, C₆₋₁₂aryl, C₁₋₈alkyl, C₇₋₁₂aralkyl, a five- or six-membered heterocycle, or a five- or six membered heterocycle fused to phenyl; or wherein *R_e* or *R_f* form a 3-8 membered nitrogen-containing heterocyclic alkyl with *R_a* or *R_b*; and wherein each *R_e* and *R_f* are optionally substituted with up to three substituents independently selected from *R₄*,

wherein the estrogen-related condition is breast cancer or bone cancer.

42. (Canceled)